

### **REMARKS**

Claims 1, 28 and 55 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner has asserted that the phrase is “a substrate of transglutaminase” is not sufficient to meet the written description requirement.

Without conceding the correctness of this rejection, Applicant has rewritten independent claims 1, 28 and 55 as new claims 140, 147 and 154 and has added to these claims limitations of canceled claims. It is believed that the additional limitations in the newly presented claims overcome the rejection. It is requested, respectfully, that this rejection be withdrawn.

Claim 1 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner has noted that the phrase “wherein the free hyaluronic acid and the conjugate are present in a molar ratio of at least 2” does not specify whether the amount of free hyaluronic acid belongs in the numerator or the denominator. Applicant has amended claim 1 to make it clear that the “free hyaluronic acid” is the numerator of the fraction. It is requested, respectfully, that this rejection be withdrawn.

The Examiner has rejected claims 28 and 55 under 35 U.S.C. § 102(b) as being anticipated by Asayama. Applicant respectfully requests reconsideration and withdrawal of this rejection, particularly in view of the amendments to the claims.

Applicant agrees that Asayama teaches hyaluronic acid covalently coupled with polylysine. Asayama teaches using its conjugate as a substrate for DNA. When combined with the conjugate, the DNA will non-covalently associate with the conjugate. The complexed material (conjugate plus DNA) then is intended to be delivered for the purpose of targeting DNA to the liver. In particular, on page 476, column 2, Asayama states “liver sinusoidal endothelial cells (SECs) possess the receptors that recognize and internalize HA... We have therefore chosen HA as the ligand for delivering the DNA to the SEC. Our recent study shows that the complexes between PLL-HA conjugates and reporter genes were distributed exclusively in SECs, leading to gene expression *in*

*vivo*.” Asayama does not teach using such a composition *per se* as a pharmaceutical for any purpose.

New claim 147 corresponds to canceled claim 28 and is directed to a pharmaceutical composition for treating dryness comprising a solution containing an effective amount of the conjugates of the invention. Claim 147 also requires that the linking molecule (e.g., polylysine) is “uncomplexed” (e.g., with DNA) in that pharmaceutical composition. Asayama does not disclose a pharmaceutical composition as described and claimed in claim 147. Asayama does not disclose a pharmaceutical composition that is uncomplex with DNA. And Asayama does not disclose a pharmaceutical composition for treating dryness and containing an effective amount of the conjugates of the invention.

New claim 154 corresponds to canceled claim 55 and describes a product for treating dry eye. The product is an eye dropper bottle containing an effective amount of a conjugate of the invention. The linking molecule of the conjugate is uncomplexed (e.g., uncomplexed to DNA). Asayama does not disclose or suggest the product of claim 154. Asayama does not disclose an eye dropper bottle of any sort, and there would be no reason to place the material of Asayama into an eye dropper bottle. It is believed that the claims, particularly as amended, are novel in view of Asayama, and it is requested, respectfully, that the 35 U.S.C. § 102(b) rejection be withdrawn.

The Examiner rejected claim 28 and 55 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 6,267,957. Reconsideration and withdrawal of the rejection is respectfully requested, particularly in view of the amendments to the claims.

U.S. Patent 6,267,957 teaches, among other things, conjugates of polylysine and various agents. One such agent is a “tissue sealant”. According to column 13 of U.S. Patent 6,267,957, “tissue sealants are those used in wound healing to mechanically seal wounds”. Respectfully, U.S. Patent 6,267,957 does not render obvious the claimed invention.

New claim 147 corresponds to canceled claim 28 and is directed to a pharmaceutical composition for treating dryness comprising a solution containing an effective amount of hyaluronic acid covalently linked to a linking molecule, such as polylysine. U.S. Patent 6,267,957 does not disclose such a pharmaceutical composition. The '957 patent does not suggest (i) a pharmaceutical preparation for treating dryness; (ii) a solution of a hyaluronic acid-polylysine conjugate; and (iii) an effective amount of the conjugate for treating dryness. New claim 154 corresponds to canceled claim 55 and is directed to an eye dropper bottle containing a solution with an effective amount of a conjugate of the invention for treating dry eye. The '957 patent does not show or suggest that the tissue sealant for mechanically sealing wounds has any utility in the eye and certainly does not suggest use of an eye dropper bottle. The '957 patent does not suggest a solution for treating dry eye or an effective amount of a conjugate of hyaluronic acid and a linking molecule for treating dry eye.

In view of the foregoing remarks it is respectfully requested that the Examiner withdraw the rejections on the basis of U.S. Patent 6,267,957 alone.

Claim 1 (which corresponds to new claim 140) stands rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 6,267,957 in view of U.S. Patent 5,770,628. According to the Examiner, the '628 patent teaches an ophthalmic formulation containing free hyaluronic acid, wherein the formulation is used as artificial tears. According to the Examiner, the hyaluronic acid is added as a viscosity enhancer.

Respectfully, the Examiner has not presented a *prima facie* basis for rejecting claim 1 (or new claim 140). The '957 patent relates in pertinent part to "tissue sealants for mechanically sealing tissue". The '628 patent, on the other hand, relates to artificial tears. First, there is no teaching in the '957 patent that the tissue sealants are useful in the eye. Secondly, there is no teaching in the '628 patent that the free hyaluronic acid which thickens artificial tears would have any application in the arena of tissue sealants. There simply is no reason to combine these two references, other than through hindsight analysis.

It is respectfully requested that the rejection based on the combination of the '957 patent and the '628 patent be withdrawn.

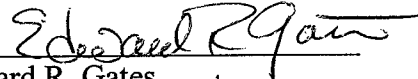
**CONCLUSION**

Claims 140-159 are pending. It is believed that all the rejections of record have been addressed. It is requested a Notice of Allowance be issued.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 23/2825 under Docket No. H0535.70016US00 from which the undersigned is authorized to draw.

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Respectfully submitted,

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